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MAY 13 2008

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In Re: Patent Term Extension
Application for
U.S. Patent No. 6,034,267

FINAL DECISION REGARDING PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C. § 156 FOR U.S. PATENT NO. 6,034,267

This is in response to the application for extension of the term of U.S. Patent No. 6,034,267 ("the '267 patent") filed under 35 U.S.C. § 156 in the United States Patent and Trademark Office ("USPTO") on September 22, 2004 ("the PTE Application"), and the Request for Reconsideration of Final Determination of Ineligibility for Patent Term Extension filed on November 13, 2007 ("the Request for Reconsideration"). The PTE Application was filed by PhotoCure ASA ("Applicant"), assignee and owner of the '267 patent. Extension was sought based upon the premarket review of METVIXIA™ (methyl aminolevulinate hydrochloride) under section 505(b) of the Federal Food Drug and Cosmetic Act ("FFDCA"). Because the Food and Drug Administration ("FDA") and the USPTO have determined that the approval of METVIXIA™ (methyl aminolevulinate hydrochloride) does not constitute the first permitted commercial marketing or use of the "product," the PTE Application is **DENIED** and the Request for Reconsideration is **DENIED**.

A. Factual Background

On July 27, 2004, the FDA approved NDA No. 21-415 for METVIXIA™ (methyl aminolevulinate hydrochloride).

On September 22, 2004, Applicant timely filed the PTE Application in the USPTO.

On November 7, 2006, the USPTO sent a letter to FDA, requesting the FDA's assistance in confirming that (1) the product identified in the PTE Application, METVIXIA™ (methyl aminolevulinate hydrochloride), was subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first permitted commercial marketing or use and (2) the PTE application was filed within the sixty-day period beginning on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use, as required by 35 U.S.C. § 156(d)(1). The November 7, 2006, letter notes at page 2 that "[a]minolevulinic acid hydrochloride had been previously approved by the FDA" and that "methyl aminolevulinate hydrochloride is an ester of aminolevulinic acid hydrochloride."

On March 5, 2007, FDA responded to the USPTO stating (1) FDA's approval of

METVIXIA™ (methyl aminolevulinate hydrochloride) does not represent the first permitted commercial marketing or use of the "product," as defined under 35 U.S.C. § 156(f)(1), and as interpreted by the courts, and (2) the PTE Application was timely filed.

On April 11, 2007, the USPTO mailed a Notice of Final Determination – Ineligible ("Notice") in which the USPTO states that the '267 patent is ineligible for patent term extension under 35 U.S.C. § 156. In particular, the Notice states:

> By the explicit terms of section 156(f)(2), the term "product" as it relates to a human drug product means the active ingredient of the new drug product. The active ingredient in the approved product METVIXIA™ is methyl aminolevulinate hydrochloride, which, as an ester of the previously-approved aminolevulinic acid hydrochloride, is by statute the same product as aminolevulinic acid hydrochloride. ... Furthermore, the prior approval of the active ingredient aminolevulinic acid hydrochloride in LEVULAN® by the Food and Drug Administration was under section 505 of the FFDCA, the same provision of law under which regulatory review of the product METVIXIA™ occurred.

On November 13, 2007, Applicant filed the Request for Reconsideration. The Request for Reconsideration states at page 3 that "the proper inquiry is simply, based on the plain language of the statute, whether or not the active ingredient in Levulan®, namely, aminolevulinic acid hydrochloride, is an ester (or the same as or a salt) of the active ingredient of Metvixia™." The Request for Reconsideration further states the following, at the paragraph bridging pages 3 and 4:

> the active ingredient of Metvixia™ is the hydrochloride salt of the ester methyl aminolevulinate, whereas the active ingredient of Levulan® is the hydrochloride salt of the acid aminolevulinic acid. Aminolevulinic acid hydrochloride is not the same as, or a salt or ester of, methyl aminolevulinate hydrochloride. The product methyl aminolevulinate hydrochloride therefore has not been previously approved because aminolevulinic acid hydrochloride does not "[fall] within the definition" of "product" as that term is properly construed. *See* [*Glaxo Operations UK, Ltd v. Quigg*, 894 F.2d 392, 394 (Fed. Cir. 1990)]. It therefore follows that Metvixia™ is not precluded from patent term extension eligibility by the previous approval of aminolevulinic acid hydrochloride.

(Emphasis in the original). The Request for Reconsideration also states at page 5 that "there are substantial differences between methyl aminolevulinate hydrochloride and [5-aminolevulinic acid ("ALA")] hydrochloride, as evidenced by the attached Declaration of Dr. Kristian Berg in Support of Grant of Patent Term Extension with Respect to U.S. Patent No. 6,034,267 and accompanying exhibits."

B. Decision

1. The Plain Language of 35 U.S.C. § 156(f) Shows That METVIXIA™ (methyl aminolevulinate hydrochloride) Is Not the First Permitted Commercial Marketing or Use of the "Product" As Required by 35 U.S.C. § 156(a)(5)(A)

Section 156(a) of Title 35 sets forth several requirements that must be met before the Director can extend the term of a patent. *See* 35 U.S.C. §§ 156 (a)(1)-(a)(5), (d)(1), & (e)(1). Section 156(a)(5)(A) requires that:

> the permission for the commercial marketing or use of the product ... [be] the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

(Emphasis added). The term "product" as used in section 156(a)(5)(A) is defined in section 156(f)(1) as a "drug product," and the term "drug product" is defined in section 156(f)(2) as the "active ingredient of [a] new drug, antibiotic drug, or human biological product ... including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." 35 U.S.C. § 156(f) (emphasis added). Hence, by the explicit terms of section 156(f)(2), the term "product" as used in section 156 includes: (i) a non-salified and non-esterified form of a molecule (*i.e.*, the "active ingredient"); (ii) any salt of the molecule (*i.e.*, the "salt ... of the active ingredient"); and (iii) any ester of the molecule (*i.e.*, the " ... ester of the active ingredient").[1] Because a "product" includes all three forms, any salt of a molecule is statutorily the same "product" as any ester of the molecule for purposes of the patent term extension provisions in section 156. Further, the plain meaning of the phrase "any ester" encompasses any ester, including salified and non-salified esters.

Prior to the approval of METVIXIA™ (methyl aminolevulinate hydrochloride), the FDA approved LEVULAN® (aminolevulinic acid hydrochloride). There is no dispute that ALA is present in both METVIXIA™ and LEVULAN® as the underlying molecule. For example, at page 2 of the Declaration attached to the Request for Reconsideration, Dr. Berg states that METVIXIA™ "has as its active ingredient the hydrochloride salt of the methyl ester of ALA," and that LEVULAN® "has the hydrochloride salt of ALA as its active ingredient." Consequently, the approved "product" is the same for both METVIXIA™ and LEVULAN® under section 156, *i.e.*, ALA merely formulated differently in each product. The later approved METVIXIA™ (methyl aminolevulinate hydrochloride) thus does not represent the first permitted commercial marketing or use of the "product" under the provision of law under which such regulatory review occurred. The USPTO therefore concludes that the PTE Application does not

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[1]The plain language of section 156(f) makes clear that the same definition of "product" is to be applied throughout section 156. Section 156(f) explicitly states that its provisions are "for purposes of this section." Thus, the term "product" as used throughout 35 U.S.C. § 156—for eligibility under section 156(a) and for enforcement under section 156(b)—has but one meaning.

satisfy the requirement of section 156(a)(5)(A) and the '267 patent is ineligible for a patent term extension. Accordingly, the PTE Application must be **DENIED**.

2. Judicial Precedent Confirms That METVIXIA™ (methyl aminolevulinate hydrochloride) Is Not the First Permitted Commercial Marketing or Use of the "Product" As Required by 35 U.S.C. § 156(a)(5)(A)

Judicial precedent confirms that the USPTO's application of the definition of "product," as that term is used in section 156(a)(5)(A), is correct. In *Fisons v. Quigg*, 1988 WL 150851 (D.D.C. 1988) ("*Fisons I*"), the district court addressed the meaning of the term "product." The district court considered both the plain language of section 156(a)(5)(A) and its legislative history. With respect to the latter, the district court observed:

> Upon examination, the specific purpose of Section 156(a)(5)(A) appears to have been relatively narrow—to restore lost patent life only for "pioneer" drugs. A report by the Congressional Office of Technology Assessment ("OTA") to the 97th Congress provided the factual foundation for the restriction of patent restoration benefits to new chemical entities. The OTA report stated: "Although important pharmaceutical innovations may result from new therapeutic applications of existing chemicals ... many of the pharmaceutical breakthroughs that have occurred have resulted from NCE (new chemical entity) research and the development of NCEs generally has required more time and money than other types of innovation and has involved greater risks." The House Committee on Energy and Commerce explained that the bill "requires extensions to be based on the first approval of the product because the only evidence available to Congress showing that patent time has been lost is data on so-called class I, new chemical entity drugs."

Fisons I, 1988 WL 150851 at *7. After making these observations, the district court found that "Congress's intent was to restore patent life only to new chemical entities." The district court thus construed section 156(a)(5)(A) in a straightforward way:

> In the definitional provision of Section 156, the term "product" is defined as a "human drug product." 35 U.S.C. § 156(f)(1)(A). This term is further defined in the next subparagraph as "the *active ingredient* of a new drug, antibiotic drug, or human biological product ... including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." 35 U.S.C. § 156(f)(2) (emphasis added in original). Substituting this definition directly back into Section 156(a)(5)(A) yields the statement that a patent is ineligible for extension if it is not the first permitted commercial marketing or use of the active ingredient contained in that approved patented product.

Id. at *5.

The Federal Circuit affirmed the district court's interpretation. *See Fisons v. Quigg*, 876 F.2d 99 (Fed. Cir. 1989) ("*Fisons II*"). The Federal Circuit stated: "In sum, we hold that the district court correctly applied the definition given in 35 U.S.C. § 156(f) to the term 'product' used in section 156(a)(5)(A). We are convinced that such an interpretation comports with the intent of Congress as expressed in the statute." *Fisons II*, 876 F.2d at 102.

The Federal Circuit later interpreted the term "active ingredient" in *Pfizer, Inc. v. Dr. Reddy's Labs.*, Ltd., 359 F.3d 1361 (Fed. Cir. 2004). There, the Federal Circuit accepted the FDA's definition of the term "active ingredient" as meaning "active moiety." *See id.* at 1366 (citing Abbreviated New Drug Application Regulations: Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,358 (F.D.A. Oct. 3, 1994)). It likewise accepted that "active moiety" means "the molecule or ion excluding those appended portions of the molecule that cause the drug to be an ester, salt ... responsible for the physiological or pharmacological action of the drug substance," based upon the FDA's regulations. *Id.* (quoting 21 C.F.R. § 314.108(a)) (omission in original). Hence, the Federal Circuit has construed the term "active ingredient" as used in section 156(f)(2) to mean the underlying molecule, *i.e.*, the molecule or ion responsible for the physiological or pharmacological action of the drug, excluding those appended portions of the molecule that cause the drug to be an ester or salt.

Substituting this definition for the word "active ingredient" as it appears in section 156, the term "drug product" in section 156(f)(2) must mean the underlying molecule as well as any salt or ester of the underlying molecule, since it is defined as "active ingredient ... including any salt or ester of the active ingredient." Further, because "product" is defined as "drug product" in section 156(f)(1)(A), "product" likewise must mean the underlying molecule as well as any salt or ester of the underlying molecule. That definition conforms with the plain language of section 156(f). What is more, the Federal Circuit confirmed in *Pfizer* that only the first approval for any given "active ingredient" can trigger a patent term extension under 35 U.S.C. § 156, regardless of whether that first approval was for an underlying molecule, a salt of the underlying molecule, or an ester of the underlying molecule. *See Pfizer*, 359 F.3d at 1366 ("The statute [referring to 35 U.S.C. § 156] foresaw variation in the salt or ester of an active ingredient, and guarded against the very loophole now urged.").

Here, before approving METVIXIA™ (methyl aminolevulinate hydrochloride) in 2004, the FDA approved LEVULAN® (aminolevulinic acid hydrochloride) in 1999. As explained above, ALA is the underlying molecule in both METVIXIA™ and LEVULAN®. ALA is simply formulated differently in the two different drugs: as a hydrochloride salt of its methyl ester in METVIXIA™, and as a hydrochloride salt in LEVULAN®. However, the difference in formulation does not matter for purposes of defining a product in section 156. The statutory definition of "product" includes the underlying molecule as well as any salt or ester of the underlying molecule. Accordingly, METVIXIA™ (methyl aminolevulinate hydrochloride) is not the first permitted commercial marketing or use of the "product" as required by 35 U.S.C. § 156(a)(5)(A) because of the earlier approval of LEVULAN® (aminolevulinic acid hydrochloride).

Finally, the FDA has issued a regulation defining the term "active ingredient" of a pharmaceutical "product" for purposes of patent term extension under 35 U.S.C. § 156. Specifically, 21 C.F.R. § 60.1(a) states that "[t]his part [referring to Part 60] sets forth procedures and requirements for the [FDA]'s review of applications for the extension of the term of certain patents under 35 U.S.C. § 156." That provision further states that "[FDA] actions in this area include [*inter alia*] [a]ssisting the [USPTO] in determining eligibility for patent term restoration." 21 C.F.R. § 60.1(a)(1). Section 60.3 then provides a series of definitions to be used in Part 60 in addition to the definitions already contained in 35 U.S.C. § 156. 37 C.F.R. § 60(b)(2) defines "active ingredient" for purposes of a patent extension to mean a drug's active moiety, *i.e.*, its therapeutically active component. It states:

> Active ingredient means any component that is intended to furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body of man or of animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

21 C.F.R. § 60.3 (b)(2). Applying the FDA's regulations in this case, ALA is the "active ingredient" of not just LEVULAN® (aminolevulinic acid hydrochloride), but also of METVIXIA™ (methyl aminolevulinate hydrochloride); it is simply formulated as a hydrochloride salt of its methyl ester in METVIXIA™, and as a hydrochloride salt in LEVULAN®.

The USPTO recognizes that *Glaxo* also concerns section 156(f). However, the USPTO observes that *Glaxo* is factually distinguishable because the Federal Circuit did not address the definition of "active ingredient" in that case. Rather, the Federal Circuit focused on the USPTO's argument that the term "product" did not have the literal meaning set forth in section 156(f)(2), but instead meant "any 'new chemical entity,' *i.e.*, 'new active moiety.'" Rejecting that argument, the Federal Circuit explained that Congress provided a definition of the term "product" in section 156(f)(2) and that Congress "selected terms with narrow meanings that it chose from among many alternatives." *Glaxo*, 894 F.2d at 399 (footnoting as examples of other possible words "new molecular entity," "active moiety," and "new chemical entity"). The Federal Circuit did not discuss the definition of the term "active ingredient" because, unlike here, the determination of the active ingredient was not in dispute in *Glaxo*.

The most that can be said about *Glaxo* is that the Federal Circuit acknowledged that the term "product" was not expressly defined by Congress to mean "active moiety," since those words do not appear in section 156(f)(2). However, *Glaxo* does not hold that the term "active ingredient" as used in section 156(f)(2) does not mean "active moiety." In fact, the Federal Circuit later accorded the term "active ingredient" with that precise definition in *Pfizer*. *See Pfizer*, 359 F.3d at 1366. Accordingly, the USPTO's determination that the '267 patent is

ineligible for extension pursuant to section 156 is supported by, and consistent with, *Glaxo*. As such, the PTE Application must be **DENIED**.

3. Applicant's Argument That METVIXIA™ Is Eligible for Patent Term Extension Because Neither Methyl Aminolevulinate Hydrochloride nor Any Salt or Ester of Methyl Aminolevulinate Hydrochloride Has Been Previously Approved for Commercial Marketing or Use Is Unpersuasive

Applicant states at page 3 of the Request for Reconsideration that "the proper inquiry is simply, based on the plain language of the statute, whether or not the active ingredient in Levulan®, namely, aminolevulinic acid hydrochloride, is an ester (or the same as or a salt) of the active ingredient of Metvixia™." At the paragraph bridging pages 3 and 4 of the Request for Reconsideration, Applicant concludes that the '267 patent is eligible for extension, because "[a]minolevulinic acid hydrochloride is not the same as, or a salt or ester of, methyl aminolevulinate hydrochloride."

In making the above statements in the Request for Reconsideration, Applicant ignores both (i) the full scope of the relationship between aminolevulinic acid hydrochloride and methyl aminolevulinate hydrochloride, and (ii) the Federal Circuit's decision in *Pfizer* that the term "active ingredient," when properly construed, means the underlying molecule, *i.e.*, the molecule or ion responsible for the physiological or pharmacological action of the drug, excluding those appended portions of the molecule that cause the drug to be an ester or salt. Applying the Federal Circuit's construction of the term "active ingredient" in *Pfizer* to the present case, ALA is the "active ingredient" of both METVIXIA™ and LEVULAN®. Consequently, the active ingredient in METVIXIA™ - ALA formulated as a hydrochloride salt of its methyl ester - has already been approved by the FDA with the approval of LEVULAN® (ALA formulated as a hydrochloride salt). Applicant's statement that neither methyl aminolevulinate hydrochloride nor an ester or salt of methyl aminolevulinate hydrochloride had previously been approved, while correct, is irrelevant to the calculus here. The USPTO must therefore conclude that the PTE Application does not satisfy the requirement of section 156(a)(5)(A) and the '267 patent is ineligible for a patent term extension. Accordingly, the PTE Application must be **DENIED**.

4. Applicant's Argument That There Are Substantial Differences Between Methyl Aminolevulinate Hydrochloride and Aminolevulinic Acid Hydrochloride Is Unpersuasive

Applicant states the following at page 5 of the Request for Reconsideration:

> there are substantial differences between methyl aminolevulinate hydrochloride and ALA hydrochloride, as evidenced by the attached Declaration of Dr. Kristian Berg in Support of Grant of Patent Term Extension with Respect to U.S. Patent

No. 6,034,267 and accompanying exhibits. These include substantial differences in selectivity of uptake by target lesions, penetration of target lesions, (unwanted) systemic distribution, pain resulting from use in PDT, and mechanisms of cell uptake. Accordingly, methyl aminolevulinate hydrochloride should not be considered the same "product" as aminolevulinic acid hydrochloride (regardless of how "product" is construed).

The existence of "substantial differences" between methyl aminolevulinate hydrochloride and aminolevulinic acid hydrochloride, even if verified, has no bearing on whether the PTE Application satisfies the requirement of section 156(a)(5)(A). For the reasons stated in the analysis above, the approved "product" is the same for both METVIXIA™ and LEVULAN® under section 156, *i.e.*, ALA merely formulated differently in each product. Nothing in the statutory language of 35 U.S.C. § 156 or in judicial precedent considering section 156 creates a "substantial differences" exception in the inquiry of whether the requirement of section 156(a)(5)(A) has been satisfied. For the reasons stated earlier herein, the USPTO concludes that the PTE Application does not satisfy the requirement of section 156(a)(5)(A) and the '267 patent is ineligible for a patent term extension. Therefore, the PTE Application must be **DENIED**.

5. Conclusion

For the reasons stated above, Applicant's request for extension of the patent term of the '267 patent is **DENIED**, and Applicant's Request for Reconsideration is **DENIED**.

This is considered a final agency decision.

Any correspondence with respect to this matter should be addressed as follows:

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Attention: Beverly Friedman

RE: METVIXIA™ (methyl aminolevulinate hydrochloride)
FDA Docket No.: 2007E-0001